NOVEL DAMMARANE SAPOGENINS, THEIR USE AS ANTI-CANCER AGENTS, AND A PROCESS FOR PRODUCING SAME

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FIELD OF THE INVENTION

[0001] This invention relates to novel dammarane sapogenins, their use in anti-cancer applications, and a process of producing the dammarane sapogenins. More particularly, the invention pertains to a novel group of dammarane sapogenins obtained by chemical cleavage of dammarane saponins extracted from panax ginseng, panax quinguefol, panax notoginseng and other species in the ginseng family, and a novel preparation of anticancer agent containing one or more of these novel sapogenins for the treatment of cancer, particularly multi-drug resistant cancers, as well as a process for producing these novel sapogenins.

BACKGROUND OF INVENTION AND RELATED ART

[0002] Since the beginning of the last decade, anti-cancer research has been increasingly directed to the discovery of novel anti-cancer agents obtained from natural sources, as well as identifying and preparing synthetic compounds found in natural sources.

[0003] Ginseng saponins (dammarane saponins, also called "ginsenosides", which are effective ingredients that organically exist in panax ginseng, panax quinguefol, panax notoginseng and other species in the ginseng family) and sapogenins (those that do not naturally exist in the ginseng plant or other species in the ginseng family and can be derived only through chemical structure modification by cleavage and/or semi-synthesis of dammarane saponins), as natural-source root compounds, have been broadly researched for their anti-cancer characteristics. Some of them have been reported to have anti-cancer effects, of which, for example, ginsenoside Rh2 [3-O-β-D-glucopyranosyl-20(s)- protopanaxadiol] has been reported for its anti-cancer activities [1], including induction of differentiation and apoptosis in cancer cells [5~11], inhibition of the growth of human ovarian cancer in nude mice after oral administration [9], and the ability to inhibit the multiplication of multi-drug resistance (MDR) cancer cells while used with other chemotherapy drugs in vitro [12].

[0004] Ginsenoside Rg3 [3-O-[β-D-glucopyranosyl(1→2)-β-D-glucopyranosyl]-20(s)- protopanaxadiol] has been reported to inhibit the invasion by various cancer cells [13] and suppress the proliferation of human prostate cancer cells [14] in vitro, and to inhibit lung metastasis in mice [15] and peritoneal metastasis in rats [16].

[0005] A metabolite of ginseng saponin produced by human intestinal bacteria, Mc [20-O-[α-L-arabinofuranosyl (1→6)-β-D-glucopyranosyl]-20(s)-protopanaxadiol], has been reported to inhibit the vascularization of tumors and extravasation of cancer cells [17].

[0006] While conventional chemotherapy agents directly attack the cancer cells and exhibit severe adverse side effects, some ginseng saponins and sapogenins, as well as their intestinal bacteria metabolites, have been reported to have inhibitory effects on cancers by induction of cancer-cell apoptosis and /or by suppression of vascularization of cancers with few adverse side effects.

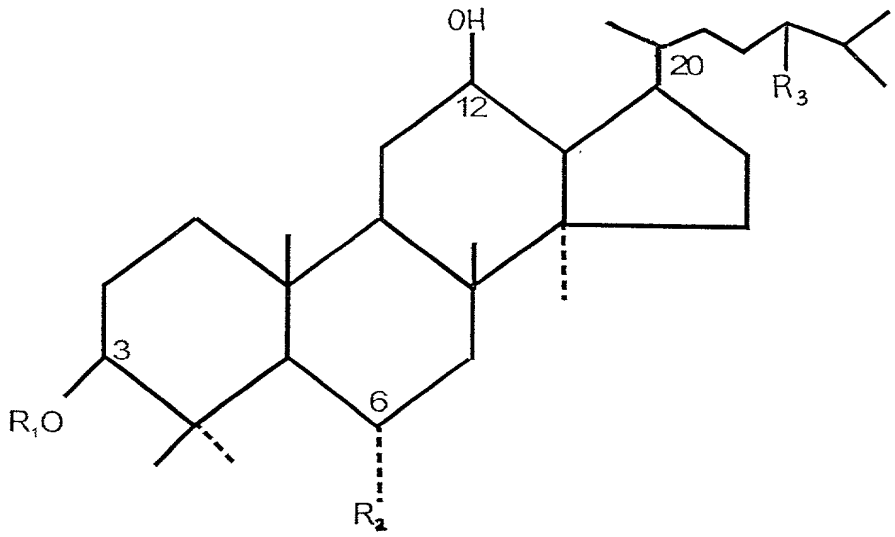
[0007] In the case of treatment of cancers with ginseng saponins, it has been reported that saponins which are metabolized to sapogenins by intestinal bacteria have anti-cancer effects. It has also been reported that ginseng saponins with a hydroxyl at C-20(R), or 20(R) epimers, such as 20(R)-Rh2 and 20(R)-Rg3 have much lower biological activities than those with a hydroxyl at C-20(S), or 20(S) epimers, such as 20(S)-Rh2 and 20(S)-Rg3 respectively. Currently, mixtures of 20(R) and 20(S) epimers are very difficult if not impossible to separate. Thus the mixture has lower efficacy than that of 20(S) epimer. Furthermore, all previously discovered ginsenosides and sapogenins either have sugar moieties at C-3, C-6 or C-20, or have a hydroxyl at C-20, or have both.

SUMMARY OF THE INVENTION

[0008] This invention relates to a group of novel sapogenins, their use in anti-cancer applications, and to a process for their production. More particularly, this invention pertains to a novel group of dammarane sapogenins, PAM-120, PBM-110 and PBM-100 (the dammarance sapogenine structure in these three sapogenins is specifically clean of any sugar moieties (glycons) at any position and a hydroxyl at C-20) and PAN-20 and PAN-30 (the dammarance sapogenin structure has sugar moieties (glycons) but is free of hydroxyl at C-20), obtained by chemical cleavage

of dammarane saponins. The invention also includes a novel application of the said sapogenins for anti-cancer treatment by using them separately or together, and/or jointly with other drugs, as well as to the process of producing these novel sapogenins. Said novel dammarane sapogenins show surprising anti-cancer effect when applied. In particular, the novel dammarane sapogenins show unexpected and superior activity against multi-drug resistant cancers.

[0009] The invention is directed to a sapogenin according to the formula:



wherein R1 is H, glc or glc^{1-2} glc, R2 is H or OH, R3 is H or OH; and when R1, R2 and R3 are H, there are double bonds at positions 20(21) and 24(25); and when R1 is H, R2 is OH and R3 is OH, there are double bonds at positions 20(22) and 25(26); and when R1 is H, R2 is OH and R3 is H, there are double bonds at positions 20(22) and 24(25); and when R1 is glc, R2 is H and R3 is H, there are double bonds at positions 20(21) and 24(25); and when R1 is glc^{1-2}glc, R2 is H and R3 is H, there are double bonds at positions 20(22) and 24(25); and pharmaceutically acceptable compositions incorporating said sapogenins.

[0010] The invention in one embodiment is directed to a sapogenin according to the formula: